Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/GB05/000367

International filing date: 03 February 2005 (03.02.2005)

Document type: Certified copy of priority document

Document details: Country/Office: GB
Number: 0405313.8
Filing date: 09 March 2004 (09.03.2004)

Date of receipt at the International Bureau: 08 April 2005 (08.04.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

GB05/367

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

I also certify that the attached copy of the request for grant of a Patent (Form 1/77) bears an amendment, effected by this office, following a request by the applicant and agreed to by the Comptroller-General.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed

Dated 18 March 2005

Patents Form 1/77
Patents Act 1977
(Rule 16)

The Patent Office

Request for grant of a patent

The Patent Office
Cardiff Road
Newport
South Wales NP10 8QQ

1. Your reference
1909401/AM

09 MAR 2004

2. Patent Application Number
0405313.8

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Sphere Medical Limited
Harston Mill
Harston
Cambridgeshire
CB2 5GG

8606295001

Patents ADP number *(if known)*

If the applicant is a corporate body, give the country/state of its incorporation

Country: **ENGLAND**
State:

4. Title of the invention

Continuous or quasi-continuous multiparametric measurement of one or more drugs and/or other clinical parameters

5. Name of agent
"Address for Service" in the United Kingdom to which all correspondence should be sent

~~**Beresford & Co**~~
~~**16 High Holborn**~~
~~**London WC1V 6BX**~~

Elkington + Fife LLP
Prospect House
8 Pembroke Rd
Sevenoaks
Kent TN13 1XR

see 5/77 9/3/05

Patents ADP number

67004

~~18260001~~

6. Priority: Complete this section if you are declaring priority from one or more earlier patent applications filed in the last 12 months.

Country	Priority application number	Date of filing

Patents Form 1/77

7. Divisionals, etc: Complete this section only if this application is a divisional application or resulted from an entitlement dispute.

Number of earlier application | Date of filing

8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request?

YES

9. Enter the number of sheets for any of the following items you are filing with this form.

Continuation sheets of this form

Description 7

Claim(s)

Abstract

Drawing(s)

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent *(Patents form 7/77)* **1 + 3 COPIES**

Request for preliminary examination and search *(Patents Form 9/77)*

Request for Substantive Examination *(Patents Form 10/77)*

Any other documents *(please specify)*

11. I/We request the grant of a patent on the basis of this application

Signature Beresford & Co Date 9 March 2004

BERESFORD & Co

12. Name and daytime telephone number of person to contact in the United Kingdom

Alan MACDOUGALL

Tel: 020 7831 2290

Continuous or quasi-continuous multiparametric measurement of one or more drugs and/or other clinical parameters

Stuart P. Hendry, Peter G. Laitenberger and Gavin. L. Troughton

Sphere Medical Limited
Harston Mill
Harston
Cambridge
CB2 5GG

Many different drugs are administered to patients in numerous clinical procedures. Dosage regimens for these drugs are usually determined from data from clinical trials that determined the average pharmacodynamic and pharmacokinetic response of the subject sample. Some drugs that are administered are required to be tightly controlled in terms of their delivery and/or bioavailability to achieve maximum therapeutic effect and minimise harmful side effects. This is particularly the case, but not exclusively so, for drugs that are used in the intensive care unit (ICU) and the operating room (OR) and that are continuously infused, but also for drugs administered by bolus or intermittently. Current practice is to take intermittent samples that, due to the expense and elaborate nature of the tests, are relatively infrequent and have significant time delays between taking the sample and receiving the result (from many hours to days). Hence, it is difficult to maintain the drug concentration within the "therapeutic window" i.e., the concentration in the plasma that is sufficiently high to have the desired pharmacological effect but not too high as to cause side effects. This can result in overdosing or inadequate dosing. Therefore, the current approach is sub-optimal as protocols have the potential to miss significant events and does not give the clinician the ability to rapidly respond to changing concentrations in the patient.

It is useful, therefore, to have knowledge of the circulating drug concentration as well as physiological parameters when seeking to treat a patient. Such drugs of interest include, but are not limited to anaesthetics such as propofol, antibiotics such as vancomycin and gentamicin and physiological parameters such as the plasma concentration as oxygen and carbon dioxide.

The invention

Currently, no product is available to enable clinicians to monitor in real-time, or close to real time, circulating analyte concentrations in particular, but not limited to, certain intravenously administered drugs notably propofol. If such drugs, including but not limited to propofol could be measured in real time, or close to real time, significant clinical benefits could be achieved. In addition, such sensors would be of significant benefit in the drug development process in pre-clinical and clinical trials.

The invention disclosed in this document provides a monitoring device that will monitor preferentially continuously, or quasi-continuously, or intermittently, or singularly in biological fluids the level or concentration of one or more drugs, pro-drugs and/or their derivatives, transition states or analytes produced as the result of the action of the

drug and/or physiological parameters. Examples of biological fluids include, but are not limited to, blood, serum, plasma, interstitial fluids, saliva, cerebrospinal fluid, breath, dialysate or other fluids, which may be optionally purified to remove, for example, red blood cells, platelets etc. The measurement approaches described are applicable to humans and animals.

Thus, it is possible to control the delivery of a drug and maintain the concentration within the therapeutic window. This is shown hypothetically in Figure 1. The actual concentration the drug can be clearly seen form trace (A) as shown by an online sensor (or any other modality that allows frequent analysis in respect to the drug pharmacokinetics and has a rapid response in respect to the changes in concentration in the patient) as proposed in this invention. It can be clearly seen that method of infrequent intermittent sampling (B) has the potential to significantly underestimate (or overestimate in certain circumstances) the circulating drug concentration and so lead to inadequate treatment. By monitoring trends in the concentration of the drugs using the sensor the dosing rate can be adjusted and /or the next therapeutic dose or delivery time and period can be determined either by the clinician or using an automated system. Thus, using the data from the sensor to control the delivery of the drug or drugs the concentration can readily be maintained within the therapeutic window thus avoiding significant over or under dosing facilitating improved treatment and optimising drug usage.

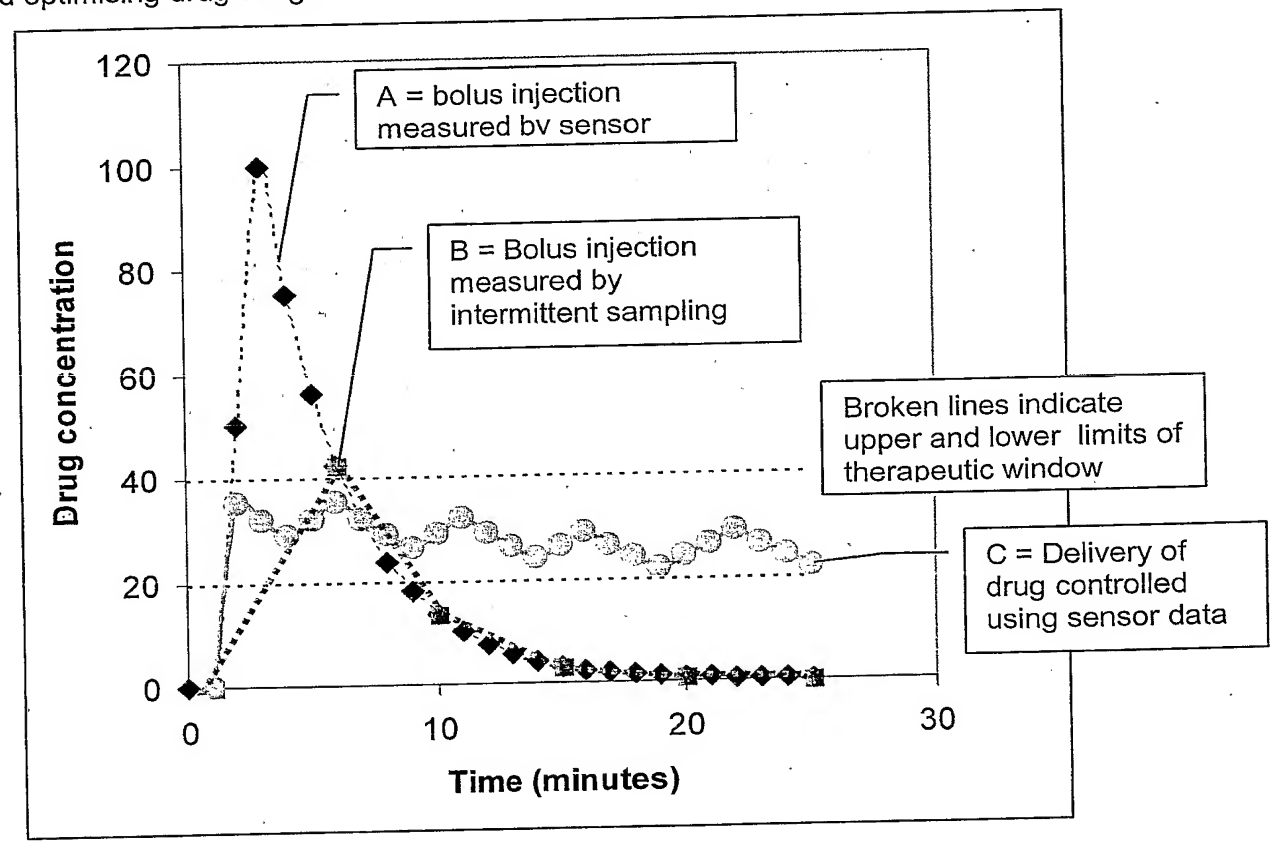

Figure 1. Conceptual advantage of closed loop drug delivery control

One embodiment of the device consists of a sensor element that is functionalised with a chemical recognition element which preferentially reacts with or binds one or more drugs being used to treat the patient, for example, but are not limited to propofol, or one or more of the drug's derivatives. The chemical recognition element may be a biologically derived substance, such as an enzyme, antibody, protein, micro-organism, cell, bacterium or virus to name but a few, or an artificial or synthetic receptor, such as a molecularly imprinted polymer (MIP). The latter are particularly attractive in the context of this invention as they have advantages with respect to biologically derived receptors in terms of robustness and cost.

The sensor can use a wide range of transduction or sensing principles to detect the interaction of the chemical recognition element with the analyte(s) of interest. Transduction principles include, but are not limited to, amperometric, conductimetric, potentiometric (in particular, ion-sensitive field effect transistor, ISFET, or chemically modified field effect transistor, CHEMFET, or more generally any device where the input is a chemical reaction or the presence of a particular chemical in close proximity to the field effect device), gravimetric, thermal, optical, resonant or surface-acoustic wave detection. One particular example is a microsensor or micromachined chip containing electrochemical transducers.

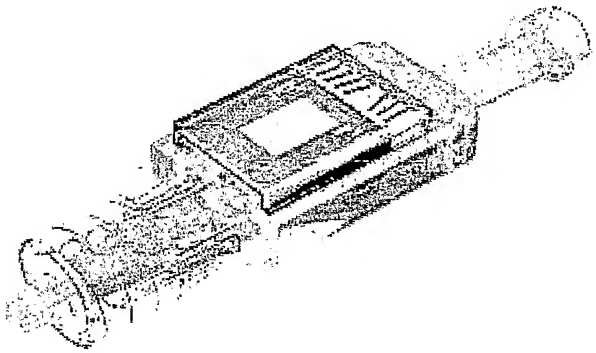

Figure 2 A patient connected analyser suitable to integrate the invention described herein.

The sensor may be combined with a sampling device that will enable the sampling of the respective fluid from the patient being treated. Of particular interest are patient-connected sampling systems, for example, an arterial or venous lines, which enable the sampling of blood from the patient (See Figure 2). Blood may be withdrawn once, repeatedly or continuously over the sensor or into a container (e.g. connected to the sensor or for transport to the sensor) in order to enable the analysis. After the analysis the blood may be returned to the patient or discharged. Other sampling methods include syringes, cranial drains (e.g. for the analysis of cerebrospinal fluid), microdialysis probes or microneedles (e.g. to access interstitial fluids and/or blood), reverse iontophoresis. Others are known to those skilled in the art.

The sensor may be configured to analyse samples from the patient repeatedly or periodically. Alternatively, it may be a configured to be used once, e.g. as a disposable or test strip. In another embodiment, the sensor is incorporated into a larger instrument, for example, an in-vitro analyser, configured to be used once or a number of times and disposed of when necessary.

The analysis can be conducted on-line, which is of particular advantage for the control of drug or therapy delivery. Alternatively, other embodiments of the invention may also be employed for off-line analysis.

The chemical recognition elements may be associated with the sensing elements in a variety of forms. They can be thin layers, in particular mono- or multilayers, of receptors or recognition elements deposited on the sensing elements. Alternatively, they may be membranes which respond to the presence of the analyte(s) or react with the analyte(s) in a known manner. Alternatively, membranes can act as filters that allow the analyte(s) to pass, while restricting the passage of other substance interfering with the measurement. The recognition elements may also take the form of particles or materials contained within or confined below a membrane. Other forms are known to those skilled in the art of preparing and using these receptor materials.

Furthermore, the chemical recognition elements may react with the analyte(s) of interest to release another substance or generate an event that is detected by the sensor element.

In some cases, further purification and concentration of the analyte(s) of interest can be achieved *in situ* by encapsulating or covering the sensing elements in one or more material(s), solid or liquid, into which the analyte(s) of interest preferentially partition(s) over the test medium it is in. One particular example, is an analyte which is in a polar test medium, but which partitions preferentially into a non-polar solvent or *vice versa*. A membrane may be used to enclose the partitioning material, if required. The membrane may be semi-permeable to the analyte(s) of interest. An illustration of one particular embodiment of this invention using this approach is shown in Figure 3.

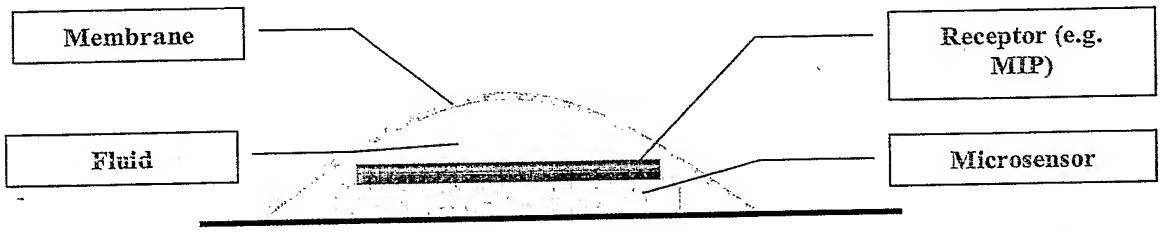

Figure 3: Schematic illustration of one particular embodiment of the invention.

One particular embodiment of the invention employs micromachined sensing elements to detect the analyte(s) of interest. Micromachined sensors are particularly attractive as they are of low cost and small size and, hence, can be used close to the patient, avoiding transport of the sample to be analysed from the patient to the analyser.

A further embodiment of the invention employs a silicon-based microsensor chip which incorporates one or more chemical sensing elements. A particular example of a multiple-analyte sensor is shown in Figure 4.

This particular chip employs potentiometric, in particular ISFETs and CHEMFETs, amperometric and conductimetric devices functionalised to the analytes of interest. However, the invention is not limited to multi-parametric micromachined chemical sensors and can employ a wide range of other microscopic and macroscopic sensors and transduction or sensing principles (see above).

The sensing elements may be functionalised to detect the analyte(s) of interest in a wide variety of ways, including, but not limited to deposition, evaporation, spin-coating, printing, ink-jet printing, dropping, spotting, centrifugation, screen printing, dripping, pipetting, droplet transfer (using e.g. a needle structure) etc. of suitable recognition elements or a mixture containing reagents which will lead to the creation of these elements.

Such a technique as described is appropriate for a number of types of drugs where knowledge of the *in vivo* concentration and/or precise control of the delivery are desirable. These include but are not limited to, anaesthetics such as propofol, analgesics, antibiotics such as vancomycin and gentamicin, immunosupressant drugs such as but not limited to cyclosporin, chemotherapy drugs for the treatment of cancers and thrombolytic drugs where the drug, an intermediate, or an analyte produced as a result of its action can be monitored.

One particular embodiment is designed for the measurement of the anaesthetic propofol and other clinically relevant parameters. The sensor consists of a receptor(s) for propofol, preferentially a molecularly imprinted polymer or another synthetic receptor or a biologically derived receptor such as an antibody or enzyme. The receptor is held in close proximity to an electrochemical or other transducer that responds to the binding of propofol to the receptor. The receptor is either in direct contact with the sample or separated from the sample by a membrane or material with physicochemical properties different from the bulk sample so that the analyte of interest diffuses from the sample into the sensor. In addition, to a sensor for propofol, sensors for other clinically important parameters can be including selected from but not limited to, temperature, pH, oxygen, carbon dioxide, glucose, lactate, fluid pressure and pharmaceutical compounds for example, antibiotics, anaesthetics. An example embodiment of such a sensor is shown in Figure 4.

The sensor gains access to the sample by virtue of being fluidically attached to, for example, an arterial line, venous line or cerebral drain. Samples can be drawn over the sensor preferentially continuously, or quasi-continuously, or intermittently, or singularly so that the sensor is exposed to the sample.

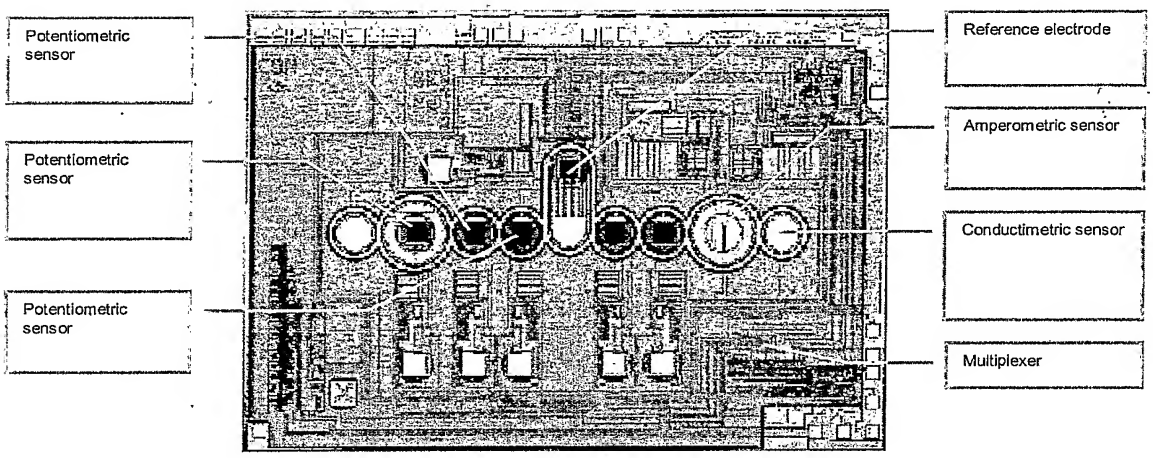

Figure 4: Example of a multi-parameter chemical sensor chip developed by Sphere Medical Ltd that could be used to measure propofol and other clinically relevant parameters.

It is desirable that such a sensor can be used to measure propofol and other clinically relevant parameters in real time, or close to real time, thereby, facilitating the accurate delivery of the drug and other therapies either via the intervention of a suitably clinically trained person such as an anaesthetist or automatically via, for example, a control loop system.

Whilst it is preferred to operate the sensor for propofol and other clinically relevant parameters in a continuous or semi-continuous manner it is possible to use this invention in a stand-alone analyser. Thus, samples are withdrawn from the patient intermittently and analysed in a device separate from the patient. The sensor in such an analyser could be reusable or disposable each sensor could be used multiple times or a separate sensor could be used for each sample.

In a stand alone analyser application the sensor would be contained in a unit which is cleaned and/or flushed at certain times between samples being analysed. Thus, the propofol bound to the receptor (MIP) would be washed off allowing the sensor to read a subsequent sample. This procedure could be repeated many times for multiple samples. It is also conceived that a stand-alone analyser could be connected to the patient using appropriate tubing to enable sampling as required.

Such a system requires a calibration routine where, samples of known analyte (propofol) concentration could be passed through the analyser intermittently, for example in between sampling blood. This calibration routine could be performed by the user, a technician, nurse or other appropriate person and/or may be automated in a suitable routine.

A further embodiment of the invention is to use the microsensor(s) in conjunction with a micro-dialysis probe. Thus, various fluids and compartments can be sampled in a non-contacting manner. Due to the size of the microsensors the dialysate volume required is kept to a minimum. Thus, the response times of a sensor used in this way can be kept at a minimum which is a significant improvement over the current art where samples are withdrawn and analysed separately with a significant time lag between sampling and analysis. Additionally, the use of a microdialysis probe allows the sensor or sensors to be readily calibrated by passing the appropriate concentration of analyte across the sensors in the dialysate.

The microdialysis probe can be placed directly in the blood, tissue, sample or body fluid or any other compartment as appropriate. It can also gain access to the sample of interest for example blood, via an arterial cannula, venous cannula or other appropriate cannula/catheter, or integrated directly into such devices.

A further invention is to use a dialysis solution in the microdialysis probe into which the analytes of interest preferentially partition from the sample medium, for example a lipid emulsion in the case of propofol.